

THE ENE REACTION OF 5-ALLYL-2 $\xi$ -HYDROXY-5 $\alpha$ -CHOLESTAN-3-ONE:  
AN UNUSUALLY FACILE ENE REACTION<sup>†</sup>

Brian A. Marples\* and Christopher D. Spilling

Department of Chemistry, The University of Technology,  
Loughborough, Leicestershire, LE11 3TU

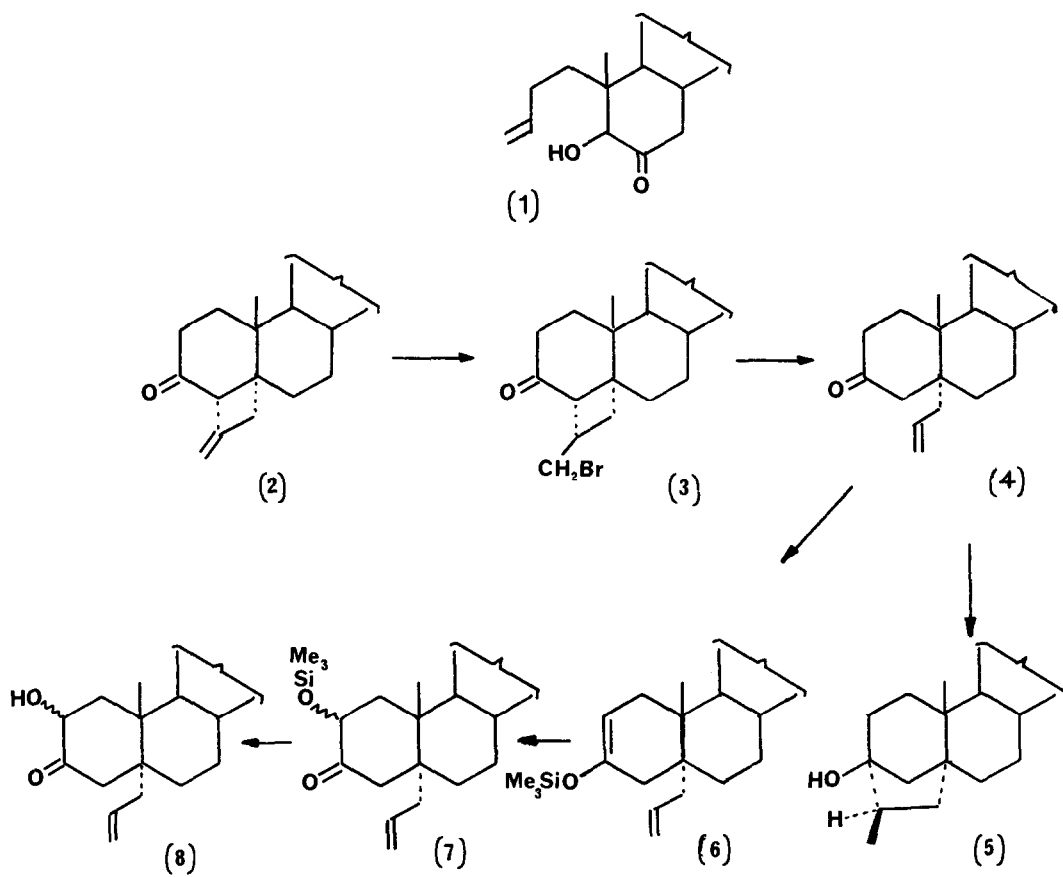
Summary The ene reaction of the unsaturated acyloins (8) occurs smoothly at 110°C demonstrating the greater reactivity of the acyloin versus the analogous ketone (4).

The unsaturated acyloin (1) undergoes an ene reaction at 200°C in decalin solution in a sealed tube.<sup>1</sup> The reaction temperature is considerably lower than for the similar ene reactions of unsaturated ketones<sup>2</sup> possibly because the ene (enediol) is electron rich relative to that (enol) in the unsaturated ketones. It was suggested that the ease with which the unsaturated acyloin (1) may achieve the required conformation for reaction may be a particularly critical factor.<sup>1</sup> Our present study with 5-allyl-2 $\xi$ -hydroxy-5 $\alpha$ -cholestan-3-one (8) confirms this view since the ene reaction proceeds smoothly at 110°C in toluene solution to afford respectively the 2,5-ethano- and the 3,5-ethano-compounds (11) and (10).

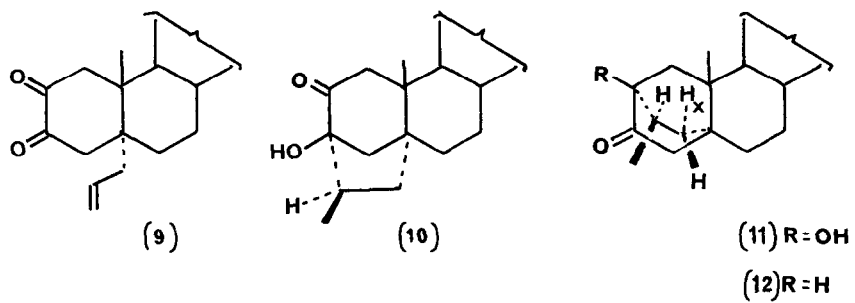
The synthesis of the required unsaturated acyloins (8) is outlined in Scheme 1.<sup>‡</sup> Photoaddition of allene<sup>3,4</sup> to cholestenone afforded the photoadduct (2) (m.p. 158-159°C,  $[\alpha]_D +62^\circ$ ) which on photobromination<sup>4</sup> gave a diastereomeric mixture of the bromoketones (3). The two diastereoisomers [(a) m.p. 128-130°C,  $[\alpha]_D +98^\circ$  and (b) m.p. 156-158°C,  $[\alpha]_D +24^\circ$ ] may be separated by flash chromatography but the mixture was treated with Li-NH<sub>3</sub>-THF<sup>4</sup> to afford 5-allyl-5 $\alpha$ -cholestan-3-one (4) (m.p. 124-125°C,  $[\alpha]_D +50^\circ$ ). A by-product of this reductive fragmentation was the bicyclic alcohol (5) (m.p. 184-185°C,  $[\alpha]_D +21^\circ$ ) also prepared directly from the allyl ketone (4) by treatment with Li-NH<sub>3</sub>-THF. It is assumed that the methyl group of the 3,5-ethano-bridge takes up the least sterically hindered configuration. Reaction of the allyl ketone (4) with Et<sub>3</sub>N-DMF-TMSCl gave the enol silyl ether (5) which on oxidation with MCPBA afforded the 2 $\xi$ -trimethylsilyloxy ketone (7).<sup>5</sup> Separation of the epimers of (7) [(a) an oil;  $\nu_{max}$  1730 cm<sup>-1</sup> (C=O) and  $\delta$ 4.07 (dd, J 3 and 7Hz, 2 $\alpha$ -H) and (b) m.p. 131-133°C,  $[\alpha]_D +36^\circ$ ;  $\nu_{max}$  1728 cm<sup>-1</sup> (C=O) and  $\delta$ 4.15 (dd, J 7 and 11Hz, 2 $\beta$ -H)] was achieved by careful flash chromatography and the non-crystalline epimer was found to be very easily hydrolysed. Deprotection of the mixed epimers of (7) with Bu<sub>4</sub>N<sup>+</sup>F<sup>-</sup> - SiO<sub>2</sub> gave the unsaturated acyloins (8) which were converted very quickly in the presence of air to the diosphenol (9) [ $\nu_{max}$  3400 (OH), 1705 (C=O) and 1665 cm<sup>-1</sup> (RCH=CH(OH)C=O)]

<sup>†</sup> Part of this work was presented at the Second International Symposium on Progress in Natural Product Chemistry, Nottingham University, July 1986.

<sup>‡</sup> Spectroscopic and analytical data, in addition to those quoted, were satisfactory for all compounds.



Scheme 1



(cf. ref. 7). Similar deprotection of the mixed epimers (7) *in situ* in toluene solution in an atmosphere of argon whilst heating under reflux (18 hours) afforded the 3,5-ethano-compound (10) (6%) (m.p. 139-141°C,  $[\alpha]_D +48^\circ$ ) and the isomeric 2,5-ethano-compound (11) (33%) (m.p. 110-112°C,  $[\alpha]_D +56^\circ$ ) which were separated by preparative t.l.c. Similar yields of (10) (7%) and (11) (27%) were obtained by heating (7) with  $\text{Bu}_4\text{N}^+\text{F}^-$ - $\text{SiO}_2$  in decalin at 200°C in a sealed tube for 4 hours. The allyl ketone (4) when similarly heated in decalin in a sealed tube at 330°C afforded the 2,5-ethano-compound (12) (79%) (m.p. 92-94°C,  $[\alpha]_D +52^\circ$ ) whereas at 250°C somewhat lower conversions (57%) were observed.

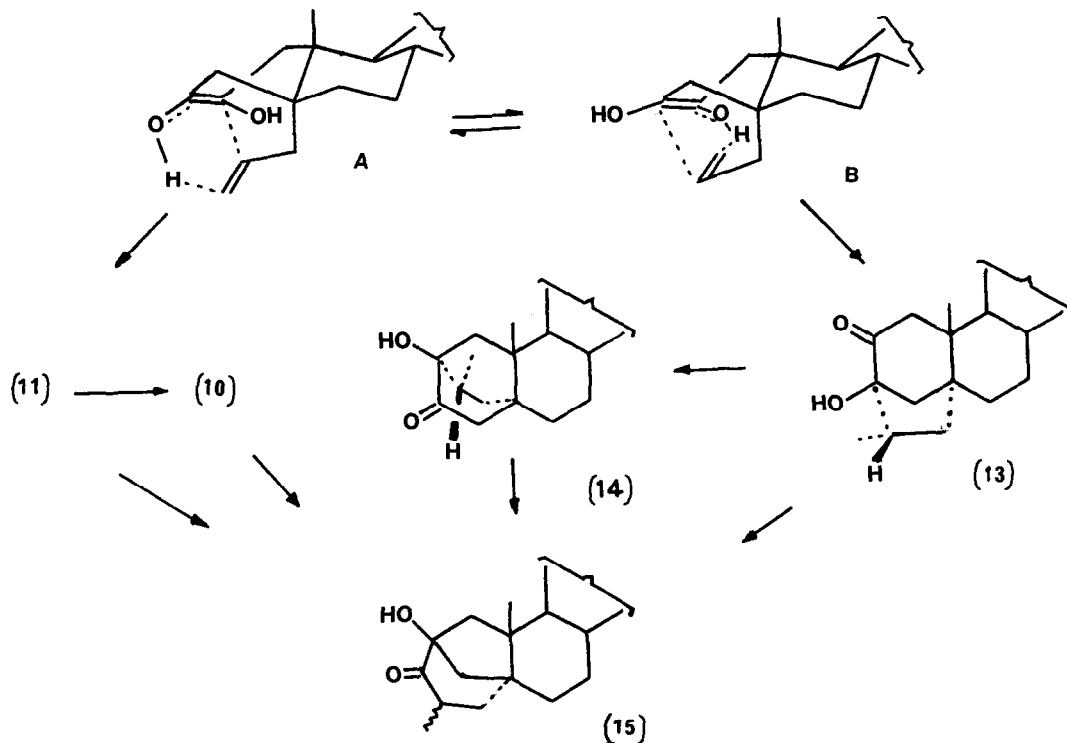
Two primary ene reaction products (11) and (13) may be formed from the unsaturated acyloins (8) arising respectively from the dienediol conformations A and B (Scheme 2). Acyloin rearrangement of (11) could afford the isomer (10) while the similar rearrangement of (13) would give (14). Other possible acyloin rearrangement products (15) may also arise in principle but the spectroscopic evidence supported the assigned structures (11) and (10). In particular, the i.r. spectrum of the major isomer (11) [ $\nu_{\text{max}}$  3500 (OH) and 1725  $\text{cm}^{-1}$  (C=O)] differed from that of (10) [ $\nu_{\text{max}}$  3495 (OH) and 1705  $\text{cm}^{-1}$  (C=O)] suggesting that the isomers differed in carbon skeleton rather than simply in the configuration of the bridge carbon atom bearing the methyl group. The 360 MHz  $^1\text{H}$  n.m.r. spectra<sup>6</sup> of (11) and (10) showed doublets (J 7Hz) for the bridge methyl groups at  $\delta$ 0.85 and 1.05 respectively. The 4-methylene group of (11) gave a double doublet at  $\delta$ 2.45 [J (gem) 19Hz and 3Hz] and a doublet at  $\delta$ 1.92 [J (gem) 19Hz]. The lower field signal is assigned to the 4 $\beta$ -H which suffers long-range (W) spin-spin coupling with the proton  $\text{H}_X$  ( $\delta$ 2.91) on the 2,5-ethano-bridge. The 1-methylene group of the 3,5-ethano-compound (10) gave an AB quartet at  $\delta$ 2.24 [J (gem) 15Hz] in which a slight broadening of the upfield branch at  $\delta$ 2.19 was observed. The absence of any detectable N.O.E. of the 1-methylene group signals on double irradiation of the bridge methyl resonance ( $\delta$ 1.05) confirmed the assigned configuration of (10) at the bridge carbon bearing the methyl group. In the alternative 3,5-ethano-compound (13) a significant N.O.E. of the 1 $\alpha$ -H signal would be predicted since the bridge methyl group is very close to the 1 $\alpha$ -H. Perhaps this steric compression is a significant factor in preventing (13) from being formed. The assignment of the structures (11) and (10) are further supported by a comparison of their  $^{13}\text{C}$  and other  $^1\text{H}$  n.m.r. data with those of (12) and (5) respectively. That the 3,5-ethano-compound (10) may be formed from the 2,5-ethano-compound (11) was demonstrated by t.l.c. of a decalin solution of the latter heated at 200°C in a sealed tube.

There is a significant difference in the temperatures required for the reaction of the allyl ketone (4) and the unsaturated acyloin (8) confirming the greater reactivity of the enediol versus the enol intermediate. It is also significant to compare the high temperature (350°C) ene reactions of the 5 $\alpha$ -vinyl-3-ketone (16).<sup>8</sup> Additionally, the relative ease of reaction of the unsaturated acyloin (8) versus that of the unsaturated acyloin (1) probably relates to the lower degree of rotational freedom of the 5 $\alpha$ -allyl group versus the 10-butenyl group thereby allowing the reacting conformations to be more readily achieved.

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## References

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Scheme 2

